Editorial

Use of patient-reported data in determining factors contributing to internal jugular vein stenosis outcomes

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The cranial and extra-cranial venous components are complex and historically under-represented part of the cerebral vascular system. However, recent development of non-invasive and reproducible venous-based ultrasound and MRI methodologies, together with the increasing availability of advanced MRI sequences suited for better evaluation of the venous system, have contributed towards greater clinical awareness and diagnosis of both intra- and extra-cranial venous pathology (1-3). Such venous abnormalities, classified as either intra- or extra-luminal defects, have been previously associated with multiple central nervous system (CNS) entities including idiopathic intracranial hypertension (IIH), Parkinson's disease, Meniere disease, multiple sclerosis, chronic migraine, transient global amnesia and headache (4-7). A step toward standardization of imaging protocols for the more accurate investigation and diagnosis of the extra-cranial venous pathology has been recently advanced by the International Society for Neurovascular Disease (ISVND) (8).

A recent report published in *Ann Transl Med* by Bai *et al.*, highlights the use of patient-reported (PRO) data in determining risk factors that may influence the treatment outcomes for internal jugular vein stenosis (IJVS) (9). The study utilized contrast-enhanced magnetic resonance venography (CE-MRV) to examine 118 patients with IJVS pathology and described series of non-neurological comorbidities and specific presenting symptoms that contributed to poorer treatment results (9). We read this comprehensive work with great interest and provide commentary on its findings, the implicated factors that influence the study outcomes and the choice of treatment, which Authors based on the specific presentations of the IJVS pathology. Lastly, the role of PROs, as emerging targets for improving the quality of the overall healthcare delivery, are discussed.

The majority of patients included in this study presented with non-thrombotic IJVS (n=105, 88.9%) with approximately equal ratio of external- and non-external etiology of the compression. Apart from outcome failures observed during stenting of the cases with IJVS who had external compression etiology, the study also reports older age, comorbid presence of diabetes mellitus type 2 and hepatitis B infection, as probable non-CNS factors contributing to poorer outcome. These findings fall in line with already established associations seen in the peripheral venous pathology (10). Furthermore, presence of intra-luminal jugular abnormalities like flaps and malformed IJV valves has been previously associated with presence of wide range of cardiovascular risk factors, including heart disease, obesity, and smoking (11,12). It has been previously reported that obesity is main risk factor for development of both diabetes mellitus type 2 and peripheral venous disease (13). All the aforementioned comorbidities do present with substantial vascular inflammation, upregulation of matrix metalloproteinase activity and activation of the coagulation cascade. Therefore, patients with already preexisting arterial disease are also predisposed to develop greater risk for venous pathology (14). Lastly, the study by Bai *et al.* also showed that older age is associated with poorer

treatment outcomes in patients with IJVS. Aging may further accelerate the cardiovascular-based inflammatory cascade, contribute to vessel wall stiffening and decrease the overall vein compliance (7). These age-associated effects on the decrease of the IJV lumen were recently seen in a longitudinal 5-year long MRV study (15). Over the follow-up period, the healthy controls demonstrated decrease of the IJV lumen from 111.9 to 99.3 mm^2 (15). Future longitudinal and population-based studies aiming to determine age-specific normative values may aid with future comparisons. The vast anatomical variability within the cerebral venous system (left to right lateralization, presence of asymptomatic venous hypoplasia) may further complicate such analyses.

Compared to the arterial counterpart, there are currently limited number of treatments for non-external IJV compression that provide sustained long-term benefit. Before the recent rise in venous stenting, balloon angioplasty was widely utilized, but limited due to high rate of re-stenosis. For example, as part of the Brain Venous Drainage Exploited Against Multiple Sclerosis (BRAVE DREAMS) trial, only 54% of patients allocated to percutaneous transluminal angioplasty had successful venous flow restoration (16). The study by Bai *et al.* had no involvement of patients with multiple sclerosis as part of the 118 subjects recruited in the study. Although venous stenting for peripheral veins is becoming more prevalent, the particular design of the stents is largely based on arterial vessel morphology and arterial hemodynamics in mind. The highly modifiable size of the IJV and subsequently large venous sinuses provide additional challenges in utilizing small diameter arterial stents. Therefore, the process of developing a venous stent would require increased flexibility that would allow sufficient anchoring and precise positioning during continuous venous pressure changes, derived from fluctuating hydrostatic and postural pressure changes. In this direction, compliant venous scaffolds like nitinol-based Petalo CVS, Veniti Vici (VENITI Inc., St. Louis, MO, USA), sinus Venous (OptiMed, Ettlingen, Germany) and Zilver Vena (Cook, Bloomington, IN, USA) stents, have been recently developed and tested (17,18). On the other hand, the report by Bai *et al.* showed that this type of venous stenting interventions does not provide sufficient clinical improvement when applied on patients with non-thrombotic IJVS with external compression etiology. The external IJVS can be either transient (due to rotational head movements and resulting compression from the sternocleidomastoid or digastric muscle) or persistent (due to compression from the bony styloid process or enlarged lymph nodes/masses in settings of malignancy) (19). In these respective jugular variants of Eagle and Bow Hunter syndrome, a surgical decompressive intervention would be more appropriate (20,21). For example, a recent report showed that patients with IIH and IJVS would additionally undergo styloidectomy, despite previous futile surgical procedures (either intracranial venous stents, CSF diversion procedures or foramen magnum decompression) (21).

The article by Bai *et al.* also describes that less than a quarter of the recruited patients present with cerebral venous sinus stenosis (CVSS) and cerebral venous sinus thrombosis (CVST). Given the accompanying findings of high rate of head noises, headache, visual disorders and tinnitus, the diagnosis of intracranial hypertension should be more carefully considered. In such cases, endovascular procedure with stenting would provide rather immediate resolution of the visual disturbances and tinnitus symptoms (22). It is unclear whether the 8 non-thrombotic IJVS patients that underwent IJV stenting and ultimately had good clinical response, were the same ones that presented with this set of symptoms and signs of intracranial hypertension. Along these lines, a recent meta-analysis did show that more than 90% patients with IIH who underwent venous sinus stenting, had full resolvement of their symptoms (23). In the context of non-CNS comorbidities, obesity is also a main risk factor in development of IIH.

Another novel aspect of the study by Bai *et al.* is the use of Patient Global Impression of Change (PGIC) scores as determinants of clinical improvement. The results are based on a scale which utilizes 7-point system that ranges from 7= very much improved, to 4= no change and 1= very much worsened symptoms. Patient-reported outcomes are becoming an essential part of the health care and have been gaining significant interest and implementation within the last decade. Taken United States as an example, the use of PROs in everyday clinic is now incentivized by both government and private insurance payers which transitions into Merit-based Incentive Payment System as part of the Affordable Care Act. That being said, healthcare providers would receive financial reimbursement based on improvement in patient-reported measures. One such initiative was undertaken by the National Institutes of Health (NIH) and the Patient-Reported Outcomes Measurement Information System (PROMIS) was instituted. More specific measures for neurological diseases (termed NIH Toolbox) allow standardized measurement of multiple aspects including

Cognition, Emotion, Motor and Sensation domains (24). Lastly, questionnaire-based Neuro-QoL™ (Quality of Life in Neurological Disorders) is one minute long standardized assessment that researchers can use in their work without any fees or royalties (25).

In conclusion, the study by Bai *et al*. showcases that isolated IJVS can be prevalent cause of multiple non-specific CNS symptoms, and proper etiology-driven treatment can result with significant clinical improvement. Factors contributing towards global vascular inflammation like aging and presence of comorbid type 2 diabetes mellitus may be partially responsible for poorer clinical outcome of IJVS cases.

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Footnote

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